# General

## Guideline Title

Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults. Management in primary, secondary and community care.

## Bibliographic Source(s)

National Collaborating Centre for Mental Health, National Collaborating Centre for Primary Care. Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults. Management in primary, secondary and community care. London (UK): National Institute for Health and Clinical Excellence (NICE); 2011 Jan. 56 p. (Clinical guideline; no. 113).

## Guideline Status

This is the current release of the guideline.

This guideline updates previous versions:

McIntosh A, Cohen A, Turnbull N, Esmonde L, Dennis P, Eatock J, Feetam C, Hague J, Hughes I, Kelly J, Kosky N, Lear G, Owens L, Ratcliffe J, Salkovskis P. Clinical guidelines for the management of anxiety. Management of anxiety (panic disorder, with or without agoraphobia, and generalised anxiety disorder) in adults in primary, secondary and community care. London (UK): National Institute for Clinical Excellence (NICE); 2004 Dec. 165 p.

National Collaborating Centre for Primary Care. Anxiety: management of anxiety (panic disorder, with or without agoraphobia, and generalised anxiety disorder) in adults in primary, secondary and community care. London (UK): National Institute for Clinical Excellence (NICE); 2007 Apr. 54 p. (Clinical guideline; no. 22).

# Recommendations

## Major Recommendations

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Collaborating Centre for Mental Health on behalf of the National Institute for Health and Clinical Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

Recommendations are marked [2004], [2004, amended 2011] or [new 2011]. [2004] indicates that the evidence has not been updated and reviewed since 2004. [2004, amended 2011] indicates that the evidence has not been updated and reviewed since 2004 but a small amendment has been made to the recommendation. [new 2011] indicates that the evidence has been reviewed and the recommendation has been updated or added.

Principles of Care for People with Generalised Anxiety Disorder (GAD)

Information and Support for People with GAD, Their Families, and Carers

When working with people with GAD:

- Build a relationship and work in an open, engaging, and non-judgemental manner.
- Explore the person's worries in order to jointly understand the impact of GAD.
- Explore treatment options collaboratively with the person, indicating that decision making is a shared process.
- Ensure that discussion takes place in settings in which confidentiality, privacy, and dignity are respected. [new 2011]

When working with people with GAD:

- Provide information appropriate to the person's level of understanding about the nature of GAD and the range of treatments available.
- If possible, ensure that comprehensive written information is available in the person's preferred language and in audio format.
- Offer independent interpreters if needed. [new 2011]

When families and carers are involved in supporting a person with GAD, consider:

- Offering a carer's assessment of their caring, physical, and mental health needs.
- Providing information, including contact details, about family and carer support groups and voluntary organisations, and helping families or carers to access these.
- Negotiating between the person with GAD and their family or carers about confidentiality and the sharing of information.
- Providing written and verbal information on GAD and its management, including how families and carers can support the person.
- Providing contact numbers and information about what to do and who to contact in a crisis. [new 2011]

Inform people with GAD about local and national self-help organisations and support groups, in particular where they can talk to others with similar experiences. [new 2011]

For people with GAD who have a mild learning disability or mild acquired cognitive impairment, offer the same interventions as for other people with GAD, adjusting the method of delivery or duration of the intervention if necessary to take account of the disability or impairment. [new 2011]

When assessing or offering an intervention to people with GAD and a moderate to severe learning disability or moderate to severe acquired cognitive impairment, consider consulting with a relevant specialist. [new 2011]

Stepped Care for People with GAD

A stepped-care model (see figure in chapter 1, section 1.2 of the short version of the original guideline document) is used to organise the provision of services and to help people with GAD, their families, carers, and practitioners to choose the most effective interventions.

Follow the stepped-care model, offering the least intrusive, most effective intervention first. [new 2011]

Step 1: All Known and Suspected Presentations of GAD

*Identification*

Identify and communicate the diagnosis of GAD as early as possible to help people understand the disorder and start effective treatment promptly. [new 2011]

Consider the diagnosis of GAD in people presenting with anxiety or significant worry, and in people who attend primary care frequently who:

- Have a chronic physical health problem or
- Do not have a physical health problem but are seeking reassurance about somatic symptoms (particularly older people and people from minority ethnic groups) or
- Are repeatedly worrying about a wide range of different issues [new 2011]

When a person with known or suspected GAD attends primary care seeking reassurance about a chronic physical health problem or somatic symptoms and/or repeated worrying, consider with the person whether some of their symptoms may be due to GAD. [new 2011]

*Assessment and Education*

For people who may have GAD, conduct a comprehensive assessment that does not rely solely on the number, severity, and duration of symptoms, but also considers the degree of distress and functional impairment. [new 2011]

As part of the comprehensive assessment, consider how the following factors might have affected the development, course, and severity of the person's GAD:

- Any comorbid depressive disorder or other anxiety disorder
- Any comorbid substance misuse
- Any comorbid medical condition
- A history of mental health disorders
- Past experience of, and response to, treatments [new 2011]

For people with GAD and a comorbid depressive or other anxiety disorder, treat the primary disorder first (that is, the one that is more severe and in which it is more likely that treatment will improve overall functioning). [new 2011] (For National Institute for Health and Clinical Excellence [NICE] guidance on depression, obsessive–compulsive disorder, and post-traumatic stress disorder see section 6 of the short version of the original guideline document. NICE is developing a guideline on identification and pathways to care for common mental health disorders. Publication expected Summer 2011.)

For people with GAD who misuse substances, be aware that:

- Substance misuse can be a complication of GAD.
- Non-harmful substance use should not be a contraindication to the treatment of GAD.
- Harmful and dependent substance misuse should be treated first as this may lead to significant improvement in the symptoms of GAD. [new 2011] (For NICE guidance on drug misuse and alcohol-use disorders see section 6 of the short version of the original guideline document. NICE is developing a guideline on the diagnosis and management of alcohol dependence and harmful alcohol use in young people and adults. Publication expected February 2011.)

Following assessment and diagnosis of GAD:

- Provide education about the nature of GAD and the options for treatment, including the 'Understanding NICE guidance' booklet (see the "Patient Resources" field).
- Monitor the person's symptoms and functioning (known as active monitoring).

This is because education and active monitoring may improve less severe presentations and avoid the need for further interventions. [new 2011]

Discuss the use of over-the-counter medications and preparations with people with GAD. Explain the potential for interactions with other prescribed and over-the-counter medications and the lack of evidence to support their safe use. [new 2011]

Step 2: Diagnosed GAD That Has Not Improved after Step 1 Interventions

*Low-intensity Psychological Interventions for GAD*

For people with GAD whose symptoms have not improved after education and active monitoring in step 1, offer one or more of the following as a first-line intervention, guided by the person's preference:

- Individual non-facilitated self-help
- Individual guided self-help
- Psychoeducational groups [new 2011]

Individual non-facilitated self-help for people with GAD should:

- Include written or electronic materials of a suitable reading age (or alternative media)
- Be based on the treatment principles of cognitive behavioural therapy (CBT)
- Include instructions for the person to work systematically through the materials over a period of at least 6 weeks
- Usually involve minimal therapist contact, for example an occasional short telephone call of no more than 5 minutes [new 2011]

Individual guided self-help for people with GAD should:

- Include written or electronic materials of a suitable reading age (or alternative media)
- Be supported by a trained practitioner, who facilitates the self-help programme and reviews progress and outcome
- Usually consist of five to seven weekly or fortnightly face-to-face or telephone sessions, each lasting 20–30 minutes [new 2011]

Psychoeducational groups for people with GAD should:

- Be based on CBT principles, have an interactive design and encourage observational learning
- Include presentations and self-help manuals
- Be conducted by trained practitioners
- Have a ratio of one therapist to about 12 participants
- Usually consist of six weekly sessions, each lasting 2 hours [new 2011]

Practitioners providing guided self-help and/or psychoeducational groups should:

- Receive regular high-quality supervision
- Use routine outcome measures and ensure that the person with GAD is involved in reviewing the efficacy of the treatment [new 2011]

Step 3: GAD with Marked Functional Impairment or That Has Not Improved after Step 2 Interventions

*Treatment Options*

For people with GAD and marked functional impairment, or those whose symptoms have not responded adequately to step 2 interventions:

- Offer either
  - An individual high-intensity psychological intervention (see recommendations below) or
  - Drug treatment (see recommendations below)
- Provide verbal and written information on the likely benefits and disadvantages of each mode of treatment, including the tendency of drug treatments to be associated with side effects and withdrawal syndromes.
- Base the choice of treatment on the person's preference as there is no evidence that either mode of treatment (individual high-intensity psychological intervention or drug treatment) is better. [new 2011]

*High-Intensity Psychological Interventions*

If a person with GAD chooses a high-intensity psychological intervention, offer either cognitive behavioral therapy (CBT) or applied relaxation. [new 2011]

CBT for people with GAD should:

- Be based on the treatment manuals used in the clinical trials of CBT for GAD
- Be delivered by trained and competent practitioners
- Usually consist of 12–15 weekly sessions (fewer if the person recovers sooner; more if clinically required), each lasting 1 hour [new 2011]

Applied relaxation for people with GAD should:

- Be based on the treatment manuals used in the clinical trials of applied relaxation for GAD
- Be delivered by trained and competent practitioners
- Usually consist of 12–15 weekly sessions (fewer if the person recovers sooner; more if clinically required), each lasting 1 hour [new 2011]

Practitioners providing high-intensity psychological interventions for GAD should:

- Have regular supervision to monitor fidelity to the treatment model, using audio or video recording of treatment sessions if possible and if the person consents
- Use routine outcome measures and ensure that the person with GAD is involved in reviewing the efficacy of the treatment [new 2011]

Consider providing all interventions in the preferred language of the person with GAD if possible. [new 2011]

*Drug Treatment*

If a person with GAD chooses drug treatment, offer a selective serotonin reuptake inhibitor (SSRI). Consider offering sertraline first because it is the most cost-effective drug, but note that at the time of publication (January 2011) sertraline did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented. Monitor the person carefully for adverse reactions. [new 2011]

If sertraline is ineffective, offer an alternative SSRI or a serotonin–noradrenaline reuptake inhibitor (SNRI), taking into account the following factors:

- Tendency to produce a withdrawal syndrome (especially with paroxetine and venlafaxine)
- The side-effect profile and the potential for drug interactions

- The risk of suicide and likelihood of toxicity in overdose (especially with venlafaxine)
- The person's prior experience of treatment with individual drugs (particularly adherence, effectiveness, side effects, experience of withdrawal syndrome, and the person's preference) [new 2011]

If the person cannot tolerate SSRIs or SNRIs, consider offering pregabalin. [new 2011]

Do not offer a benzodiazepine for the treatment of GAD in primary or secondary care except as a short-term measure during crises. Follow the advice in the 'British national formulary' on the use of a benzodiazepine in this context. [new 2011]

Do not offer an antipsychotic for the treatment of GAD in primary care. [new 2011]

Before prescribing any medication, discuss the treatment options and any concerns the person with GAD has about taking medication. Explain fully the reasons for prescribing and provide written and verbal information on:

- The likely benefits of different treatments
- The different propensities of each drug for side effects, withdrawal syndromes, and drug interactions
- The risk of activation with SSRIs and SNRIs, with symptoms such as increased anxiety, agitation and problems sleeping
- The gradual development, over 1 week or more, of the full anxiolytic effect
- The importance of taking medication as prescribed and the need to continue treatment after remission to avoid relapse [new 2011]

Take into account the increased risk of bleeding associated with SSRIs, particularly for older people or people taking other drugs that can damage the gastrointestinal mucosa or interfere with clotting (for example, non-steroidal anti-inflammatory drugs [NSAIDS] or aspirin). Consider prescribing a gastroprotective drug in these circumstances. [new 2011]

For people aged under 30 who are offered an SSRI or SNRI:

- Warn them that these drugs are associated with an increased risk of suicidal thinking and self-harm in a minority of people under 30 and
- See them within 1 week of first prescribing and
- Monitor the risk of suicidal thinking and self-harm weekly for the first month [new 2011]

For people who develop side effects soon after starting drug treatment, provide information and consider one of the following strategies:

- Monitoring the person's symptoms closely (if the side effects are mild and acceptable to the person) or
- Reducing the dose of the drug or
- Stopping the drug and, according to the person's preference, offering either
    - An alternative drug (see recommendations above) or
    - A high-intensity psychological intervention (see recommendations above) [new 2011]

Review the effectiveness and side effects of the drug every 2–4 weeks during the first 3 months of treatment and every 3 months thereafter. [new 2011]

If the drug is effective, advise the person to continue taking it for at least a year as the likelihood of relapse is high. [new 2011]

*Inadequate Response to Step 3 Interventions*

If a person's GAD has not responded to a full course of a high-intensity psychological intervention, offer a drug treatment (see recommendations above). [new 2011]

If a person's GAD has not responded to drug treatment, offer either a high-intensity psychological intervention (see recommendations above) or an alternative drug treatment (see recommendations above). [new 2011]

If a person's GAD has partially responded to drug treatment, consider offering a high-intensity psychological intervention in addition to drug treatment. [new 2011]

Consider referral to step 4 if the person with GAD has severe anxiety with marked functional impairment in conjunction with:

- A risk of self-harm or suicide or
- Significant comorbidity, such as substance misuse, personality disorder or complex physical health problems or
- Self-neglect or
- An inadequate response to step 3 interventions [new 2011]

Step 4: Complex, Treatment-Refractory GAD and Very Marked Functional Impairment or High Risk of Self-Harm (Step 4 normally refers to community mental health teams but may include specialist services and specialist practitioners in primary care.)

*Assessment*

Offer the person with GAD a specialist assessment of needs and risks, including:

- Duration and severity of symptoms, functional impairment, comorbidities, risk to self, and self-neglect
- A formal review of current and past treatments, including adherence to previously prescribed drug treatments and the fidelity of prior psychological interventions, and their impact on symptoms and functional impairment
- Home environment
- Support in the community
- Relationships with and impact on families and carers [new 2011]

Review the needs of families and carers and offer an assessment of their caring, physical, and mental health needs if one has not been offered previously. [new 2011]

Develop a comprehensive care plan in collaboration with the person with GAD that addresses needs, risks, and functional impairment and has a clear treatment plan. [new 2011]

*Treatment*

Inform people with GAD who have not been offered or have refused the interventions in steps 1–3 about the potential benefits of these interventions, and offer them any they have not tried. [new 2011]

Consider offering combinations of psychological and drug treatments, combinations of antidepressants, or augmentation of antidepressants with other drugs, but exercise caution and be aware that:

- Evidence for the effectiveness of combination treatments is lacking and
- Side effects and interactions are more likely when combining and augmenting antidepressants [new 2011]

Combination treatments should be undertaken only by practitioners with expertise in the psychological and drug treatment of complex, treatment-refractory anxiety disorders and after full discussion with the person about the likely advantages and disadvantages of the treatments suggested. [new 2011]

When treating people with complex and treatment-refractory GAD, inform them of relevant clinical research in which they may wish to participate, working within local and national ethical guidelines at all times. [new 2011]

Principles of Care for People with Panic Disorder

General Management for Panic Disorder

People who have panic disorder and their families and carers need comprehensive information, presented in clear and understandable language, about the nature of their condition and the treatment options available. Such information is essential for shared decision-making between people with panic disorder and healthcare professionals, particularly when making choices between broadly equivalent treatments. In addition, given the emotional, social, and economic costs panic disorder usually entails, people with panic disorder and their families and carers may need help in contacting support and self-help groups. Support groups can also promote understanding and collaboration between people who have panic disorder, their families, and carers, and healthcare professionals at all levels of primary and secondary care.

Shared Decision-Making and Information Provision

Shared decision-making should take place as it improves concordance and clinical outcomes. [2004]

Shared decision-making between the individual and healthcare professionals should take place during the process of diagnosis and in all phases of care. [2004]

People with panic disorder and, when appropriate, families and carers should be provided with information on the nature, course, and treatment of panic disorder, including information on the use and likely side-effect profile of medication. [2004]

To facilitate shared decision-making, evidence-based information about treatments should be available and discussion of the possible options should take place. [2004]

People's preference and the experience and outcome of previous treatment(s) should be considered in determining the choice of treatment. [2004]

Common concerns about taking medication, such as fears of addiction, should be addressed. [2004]

In addition to being provided with high-quality information, people with panic disorder and their families and carers should be informed of self-help groups and support groups and be encouraged to participate in such programmes where appropriate. [2004]

Language

When talking to people with panic disorder and their families and carers, healthcare professionals should use everyday, jargon-free language. If technical terms are used they should be explained to the person. [2004]

Where appropriate, all services should provide written material in the language of the person, and appropriate interpreters should be sought for people whose preferred language is not English. [2004]

Where available, consideration should be given to providing psychotherapies in the person's own language if this is not English. [2004]

Stepped Care for People with Panic Disorder

The guideline provides recommendations for care at different stages of the person's journey, represented as different steps:

- Step 1 – Recognition and diagnosis
- Step 2 – Treatment in primary care
- Step 3 – Review and consideration of alternative treatments
- Step 4 – Review and referral to specialist mental health services
- Step 5 – Care in specialist mental health services

Step 1: Recognition and Diagnosis of Panic Disorder

*Consultation Skills*

All healthcare professionals involved in diagnosis and management should have a demonstrably high standard of consultation skills so that a structured approach can be taken to the diagnosis and subsequent management plan for panic disorder. The standards detailed in the video workbook 'Summative Assessment For General Practice Training: Assessment Of Consulting Skills – the MRCGP/Summative Assessment Single Route' (see www.rcgp.org.uk/exam ) and required of the Membership of the Royal College of General Practitioners are a good example of standards for consulting skills. [2004]

*Diagnosis*

The accurate diagnosis of panic disorder is central to the effective management of this condition. It is acknowledged that frequently there are other conditions present, such as depression, that can make the presentation and diagnosis confusing.

The diagnostic process should elicit necessary relevant information such as personal history, any self-medication, and cultural or other individual characteristics that may be important considerations in subsequent care. [2004]

There is insufficient evidence on which to recommend a well validated, self-reporting screening instrument to use in the diagnostic process, and so consultation skills should be relied upon to elicit all necessary information. [2004]

*Comorbidities*

The clinician should be alert to the common clinical situation of comorbidity, in particular, panic disorder with depression and panic disorder with substance misuse. [2004, amended 2011]

The main problem(s) to be treated should be identified through a process of discussion with the person. In determining the priorities of the comorbidities, the sequencing of the problems should be clarified. This can be helped by drawing up a timeline to identify when the various problems developed. By understanding when the symptoms developed, a better understanding of the relative priorities of the comorbidities can be achieved, and there is a better opportunity of developing an effective intervention that fits the needs of the individual. [2004]

*Presentation in Accident and Emergency (A&E) with Panic Attacks*

It is important to remember that a panic attack does not necessarily constitute a panic disorder and appropriate treatment of a panic attack may limit the development of panic disorder. For people who present with chest pain at A&E services, there appears to be a greater likelihood of the

cause being panic disorder if coronary artery disease is not present or the person is female or relatively young. Two other variables, atypical chest pain and self-reported anxiety, may also be associated with panic disorder presentations, but there is insufficient evidence to establish a relationship.

If a person presents in A&E, or other settings, with a panic attack, they should:

- Be asked if they are already receiving treatment for panic disorder
- Undergo the minimum investigations necessary to exclude acute physical problems
- Not usually be admitted to a medical or psychiatric bed
- Be referred to primary care for subsequent care, even if assessment has been undertaken in A&E
- Be given appropriate written information about panic attacks and why they are being referred to primary care
- Be offered appropriate written information about sources of support, including local and national voluntary and self-help groups [2004]

Panic Disorder – Steps 2–5

*Step 2 for People with Panic Disorder: Offer Treatment in Primary Care*

The recommended treatment options have an evidence base: psychological therapy, medication, and self-help have all been shown to be effective. The choice of treatment will be a consequence of the assessment process and shared decision-making.

There may be instances when the most effective intervention is not available (for example, CBT) or is not the treatment option chosen by the person. In these cases, the healthcare professional will need to consider, after discussion with the person, whether it is acceptable to offer one of the other recommended treatments. If the preferred treatment option is currently unavailable, the healthcare professional will also have to consider whether it is likely to become available within a useful timeframe.

*General*

Benzodiazepines are associated with a less good outcome in the long term and should not be prescribed for the treatment of individuals with panic disorder. [2004]

Sedating antihistamines or antipsychotics should not be prescribed for the treatment of panic disorder. [2004]

In the care of individuals with panic disorder, any of the following types of intervention should be offered and the preference of the person should be taken into account. The interventions that have evidence for the longest duration of effect, in descending order, are:

- Psychological therapy (see recommendations below)
- Pharmacological therapy (antidepressant medication) (see recommendations below)
- Self-help (see recommendations below) [2004]

The treatment option of choice should be available promptly. [2004]

There are positive advantages of services based in primary care (for example, lower rates of people who do not attend) and these services are often preferred by people. [2004]

*Psychological Interventions*

CBT should be used. [2004]

CBT should be delivered only by suitably trained and supervised people who can demonstrate that they adhere closely to empirically grounded treatment protocols. [2004]

CBT in the optimal range of duration (7–14 hours in total) should be offered. [2004]

For most people, CBT should take the form of weekly sessions of 1–2 hours and should be completed within a maximum of 4 months of commencement. [2004]

Briefer CBT should be supplemented with appropriate focused information and tasks. [2004]

Where briefer CBT is used, it should be around 7 hours and designed to integrate with structured self-help materials. [2004]

For a few people, more intensive CBT over a very short period of time might be appropriate. [2004]

*Pharmacological Interventions – Antidepressant Medication*

Antidepressants should be the only pharmacological intervention used in the longer term management of panic disorder. The two classes of antidepressants that have an evidence base for effectiveness are the SSRIs and tricyclic antidepressants (TCAs).

The following must be taken into account when deciding which medication to offer:

- The age of the person
- Previous treatment response
- Risks
    - The likelihood of accidental overdose by the person being treated and by other family members if appropriate
    - The likelihood of deliberate self-harm, by overdose or otherwise *(the highest risk is with TCAs)*
- Tolerability
- *The possibility of interactions with concomitant medication (consult Appendix 1 of the 'British National Formulary')*
- The preference of the person being treated
- Cost, where equal effectiveness is demonstrated [2004; The text shown in italics in this recommendation was amended in 2007.]

All people who are prescribed antidepressants should be informed, at the time that treatment is initiated, of potential side effects (including transient increase in anxiety at the start of treatment) and of the risk of discontinuation/withdrawal symptoms if the treatment is stopped abruptly or in some instances if a dose is missed or, occasionally, on reducing the dose of the drug. [2004]

People started on antidepressants should be informed about the delay in onset of effect, the time course of treatment, the need to take medication as prescribed, and possible discontinuation/withdrawal symptoms. Written information appropriate to the person's needs should be made available. [2004]

Unless otherwise indicated, an SSRI licensed for panic disorder should be offered. [2004]

If an SSRI is not suitable or there is no improvement after a 12-week course and if a further medication is appropriate, imipramine or clomipramine may be considered. [2004] (Note: At the time of publication [January 2011] imipramine and clomipramine did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented.)

When prescribing an antidepressant, the healthcare professional should consider the following.

- Side effects on the initiation of antidepressants may be minimised by starting at a low dose and increasing the dose slowly until a satisfactory therapeutic response is achieved.
- In some instances, doses at the upper end of the indicated dose range may be necessary and should be offered if needed.
- Long-term treatment may be necessary for some people and should be offered if needed.
- If the person is showing improvement on treatment with an antidepressant, the medication should be continued for at least 6 months after the optimal dose is reached, after which the dose can be tapered. [2004]

If there is no improvement after a 12-week course, an antidepressant from the alternative class (if another medication is appropriate) or another form of therapy (see recommendation above under "General") should be offered. [2004]

People should be advised to take their medication as prescribed. This may be particularly important with short half-life medication in order to avoid discontinuation/withdrawal symptoms. [2004]

Stopping antidepressants abruptly can cause discontinuation/withdrawal symptoms. To minimise the risk of discontinuation/withdrawal symptoms when stopping antidepressants, the dose should be reduced gradually over an extended period of time. [2004]

All people prescribed antidepressants should be informed that, although the drugs are not associated with tolerance and craving, discontinuation/withdrawal symptoms may occur on stopping or missing doses or, occasionally, on reducing the dose of the drug. These symptoms are usually mild and self-limiting but occasionally can be severe, particularly if the drug is stopped abruptly. [2004]

Healthcare professionals should inform people that the most commonly experienced discontinuation/withdrawal symptoms are dizziness, numbness and tingling, gastrointestinal disturbances (particularly nausea and vomiting), headache, sweating, anxiety, and sleep disturbances. [2004]

Healthcare professionals should inform people that they should seek advice from their medical practitioner if they experience significant discontinuation/withdrawal symptoms. [2004]

If discontinuation/withdrawal symptoms are mild, the practitioner should reassure the person and monitor symptoms. If severe symptoms are

experienced after discontinuing an antidepressant, the practitioner should consider reintroducing it (or prescribing another from the same class that has a longer half-life) and gradually reducing the dose while monitoring symptoms. [2004]

*Self-Help*

Bibliotherapy based on CBT principles should be offered. [2004]

Information about support groups, where they are available, should be offered. (Support groups may provide face-to-face meetings, telephone conference support groups [which can be based on CBT principles], or additional information on all aspects of anxiety disorders plus other sources of help.) [2004]

The benefits of exercise as part of good general health should be discussed with all people with panic disorder as appropriate. [2004]

Step 3 for People with Panic Disorder: Review and Offer Alternative Treatment if Appropriate

If, after a course of treatment, the clinician and the person with panic disorder agree that there has been no improvement with one type of intervention, the person should be reassessed and consideration given to trying one of the other types of intervention. [2004]

Step 4 for People with Panic Disorder: Review and Offer Referral from Primary Care if Appropriate

In most instances, if there have been two interventions provided (any combination of psychological intervention, medication, or bibliotherapy) and the person still has significant symptoms, then referral to specialist mental health services should be offered. [2004]

Step 5 for People with Panic Disorder: Care in Specialist Mental Health Services

Specialist mental health services should conduct a thorough, holistic reassessment of the individual, their environment and social circumstances. This reassessment should include evaluation of:

- Previous treatments, including effectiveness and concordance
- Any substance use, including nicotine, alcohol, caffeine, and recreational drugs
- Comorbidities
- Day-to-day functioning
- Social networks
- Continuing chronic stressors
- The role of agoraphobic and other avoidant symptoms

A comprehensive risk assessment should be undertaken and an appropriate risk management plan developed. [2004]

To undertake these evaluations, and to develop and share a full formulation, more than one session may be required and should be available. [2004]

Care and management should be based on the individual's circumstances and shared decisions made. Options include:

- Treatment of co-morbid conditions
- CBT with an experienced therapist if not offered already, including home-based CBT if attendance at clinic is difficult
- Structured problem solving
- Full exploration of pharmaco-therapy
- Day support to relieve carers and family members
- Referral for advice, assessment, or management to tertiary centres [2004]

There should be accurate and effective communication between all healthcare professionals involved in the care of any person with panic disorder, and particularly between primary care clinicians (general practitioner and teams) and secondary care clinicians (community mental health teams) if there are existing physical health conditions that also require active management. [2004]

Monitoring and Follow-up for Individuals with Panic Disorder

*Psychological Interventions*

There should be a process within each practice to assess the progress of a person undergoing CBT. The nature of that process should be determined on a case-by-case basis. [2004]

*Pharmacological Interventions*

When a new medication is started, the efficacy and side-effects should be reviewed within 2 weeks of starting treatment and again at 4, 6, and 12 weeks. Follow the summary of product characteristics with respect to all other monitoring required. [2004]

At the end of 12 weeks, an assessment of the effectiveness of the treatment should be made, and a decision made as to whether to continue or consider an alternative intervention. [2004]

If medication is to be continued beyond 12 weeks, the individual should be reviewed at 8- to 12-week intervals, depending on clinical progress and individual circumstances. [2004]

*Self-Help*

Individuals receiving self-help interventions should be offered contact with primary healthcare professionals, so that progress can be monitored and alternative interventions considered if appropriate. The frequency of such contact should be determined on a case-by-case basis, but is likely to be between every 4 and 8 weeks. [2004]

Outcome Measures

Short, self-completed questionnaires (such as the panic subscale of the agoraphobic mobility inventory for individuals with panic disorder) should be used to monitor outcomes wherever possible. [2004]

## Clinical Algorithm(s)

None provided

# Scope

## Disease/Condition(s)

Generalised anxiety disorder and panic disorder (with or without agoraphobia)

## Guideline Category

Counseling

Evaluation

Management

Treatment

## Clinical Specialty

Emergency Medicine

Family Practice

Psychiatry

Psychology

## Intended Users

Advanced Practice Nurses

Allied Health Personnel

Emergency Medical Technicians/Paramedics

Health Care Providers

Hospitals

Nurses

Occupational Therapists

Patients

Pharmacists

Physician Assistants

Physicians

Psychologists/Non-physician Behavioral Health Clinicians

Public Health Departments

## Guideline Objective(s)

- To make recommendations for the treatment and management of generalised anxiety disorder (GAD)
- To improve access and engagement with treatment and services for people with GAD
- To evaluate the role of specific psychological and psychosocial interventions in the treatment of GAD
- To evaluate the role of specific pharmacological interventions in the treatment of GAD
- To integrate the above to provide best-practice advice on the care of people with GAD and their family and carers
- To promote the implementation of best clinical practice through the development of recommendations tailored to the requirements of the National Health Service (NHS) in England and Wales

## Target Population

Adults (aged 18 years and older) with a working diagnosis of anxiety disorder

Note: The guideline does not cover the care of the following: children and young people (aged 18 years or older) with a working diagnosis of generalised anxiety disorder. This guideline update may be relevant to adults with the following conditions, but will not specifically address panic disorder, major depression, bipolar depression, seasonal affective disorder, combat disorder, phobic disorders, obsessive compulsive disorder, post-traumatic stress disorder, and anxiety disorders associated with dementia.

## Interventions and Practices Considered

Management of Generalised Anxiety Disorder (GAD)

1. Providing information and support for people with GAD, their families and carers
2. Use of a stepped-care model of management
3. Identification and communication of diagnosis of GAD
4. Assessment and education, including assessment of comorbidities such as depression and substance abuse
5. Discussing over-the-counter medications and potential for drug interactions
6. Use of low-intensity psychological interventions (e.g., non-facilitated and guided self-help, psychoeducational groups)
7. Use of high-intensity psychological interventions (e.g., cognitive behavioural therapy, applied relaxation)
8. Drug treatment
    - Sertraline or alternative selective serotonin reuptake inhibitor (SSRI)
    - Serotonin–noradrenaline reuptake inhibitor (SNRI)

    - Pregabalin
    - Antipsychotic and benzodiazepines (considered but not recommended for use in primary care)
    - Educating patients about adverse effects of drug treatment
9. Combinations of psychological and drug treatments, combinations of antidepressants or augmentation of antidepressants with other drugs
10. Referral for specialist assessment

Management of Panic Disorder

1. Shared decision-making and information provision, with use of appropriate language
2. Use of stepped-care model of management
3. Recognition and diagnosis of panic disorder
    - Use of appropriate consultation skills
    - Accurate diagnosis of panic disorder
    - Identification of comorbidities
    - Presentation of panic disorder in accident and emergency (A&E) services
4. Treatment in primary care
    - Benzodiazepines, antihistamines, and antipsychotics (considered but not recommended)
    - Psychological interventions (cognitive behavioural therapy)
    - Drug treatment (SSRIs and tricyclic antidepressants)
    - Bibliotherapy
    - Support groups
    - Exercise
    - Review of care and offer of alternative treatment
    - Review of care and referral to specialist
5. Specialist assessment and treatment
6. Follow-up and monitoring
7. Measuring outcome through questionnaires

## Major Outcomes Considered

- Anxiety symptoms
- Quality of life
- Tolerability of treatment
- Adverse effects of treatment
- Clinical effectiveness of treatments
- Cost-effectiveness of treatment
- Quality adjusted life years

# Methodology

## Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Searches of Unpublished Data

## Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Collaborating Centre for Mental Health on

behalf of the National Institute for Health and Clinical Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

Review Questions

Review (clinical) questions were used to guide the identification and interrogation of the evidence base relevant to the topic of the guideline. For questions about interventions, the PICO (patient, intervention, comparison, and outcome) framework was used. This structured approach divides each question into four components: the patients (the population under study), the interventions (what is being done), the comparisons (other main treatment options) and the outcomes (the measures of how effective the interventions have been).

In some situations, the prognosis of a particular condition is of greater importance than its general significance in relation to specific interventions. Areas where this is particularly likely to occur relate to assessment of risk, for example, in terms of behaviour modification or screening and early intervention. To help facilitate the literature review, a note was made of the study design type that is most appropriate for answering each question.

See section 3.4 of the full version of the original guideline document for additional information on the development of review questions.

Systematic Clinical Literature Review

The aim of the clinical literature review was to systematically identify and synthesise relevant evidence from the literature in order to answer the specific review questions developed by the guideline development group (GDG). Thus, clinical practice recommendations are evidence-based, where possible, and, if evidence is not available, informal consensus methods are used.

Scoping Searches

A broad preliminary search of the literature was undertaken in April 2009 to obtain an overview of the issues likely to be covered by the scope, and to help define key areas. A second scoping search was conducted in June 2009, as a result of changes made to the scope. See section 3.5 of the full version of the original guideline document for additional information on scoping searches.

The Review Process

The previous NICE guideline on generalised anxiety disorder (GAD) and panic disorder was evaluated by the review team in liaison with NICE. It was agreed that the methodology utilised by the guideline was not consistent with the current NICE guideline manual. It was subsequently decided that the review process would consider all evidence from inception to the present date (which may include data already reviewed in the previous guideline) using methodology more consistent with the current version of the NICE guideline manual, as described in section 3.5.2 of the full version of the original guideline document.

Systematic Literature Searches

After the review questions were formulated, a systematic search strategy was developed to locate all the relevant evidence. The balance between sensitivity (the power to identify all studies on a particular topic) and specificity (the ability to exclude irrelevant studies from the results) was carefully considered, and a decision made to utilise highly sensitive strategies to identify as complete a set as possible of clinically relevant studies.

In order to ensure comprehensive coverage, search terms for GAD were kept purposely broad to help counter dissimilarities in bibliographic databases in thesaurus terms and indexing practices, and (often) imprecise reporting of study populations by authors in the titles and abstracts of records. It was observed that broader searching retrieved significantly more relevant records than would have been achieved through the use of more specific terms. A broad search for panic was similarly constructed for evidence relating to the effectiveness of computerised cognitive behavioural therapy (CCBT).

A stepwise approach to formulising the searches was implemented at all times, and attempts were made to eradicate duplication of effort in areas of overlapping coverage. Searches were restricted to systematic reviews, meta-analyses, randomised controlled trials (RCTs), and qualitative research, and were conducted in the following bibliographic databases:

- Allied and Complementary Medicine Database (AMED)
- Cochrane Database of Systematic Reviews (CDSR)
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Cumulative Index to Nursing and Allied Health Literature (CINAHL)
- EMBASE
- Health Technology Assessment (HTA) database
- International Bibliography of the Social Sciences (IBSS)
- MEDLINE/MEDLINE In-Process

- PsycINFO

Search strategies were initially developed for MEDLINE and subsequently translated for use in other databases/search interfaces.

The Search Process for Questions Concerning Interventions

For questions relating to interventions, the initial evidence base was formed from well-conducted RCTs that addressed at least one of the review questions. For other review questions, searches were conducted for the appropriate study design.

Where the evidence base was large, recent high-quality English-language systematic reviews were used primarily as a source of RCTs (see Appendix 10 of the full guideline document for quality criteria used to assess systematic reviews). However, in some circumstances existing datasets were utilised. Where this was the case, data were cross-checked for accuracy before use. New RCTs meeting inclusion criteria set by the GDG were incorporated into the existing reviews and fresh analyses performed.

*Reference Manager*

Citations from each search were downloaded into Reference Manager (a software product for managing references and formatting bibliographies) and all duplicates removed. Records were then screened against the inclusion criteria of the reviews before being quality appraised. The unfiltered search results were saved and retained for future potential re-analysis to help keep the process both replicable and transparent.

*Search Filters*

The search filters utilised in work for this guideline are adaptations of filters designed by the National Health Service (NHS) Centre for Reviews and Dissemination (CRD), the Health Information Research Unit of McMaster University, Ontario, and the University of Alberta. Each filter comprises medical subject headings (MeSH), explosions (exp), subheadings (sh), and text words (ti,ab/tw) based on various research design features and characteristics. The qualitative research filter was developed in-house. Each filter comprises index terms relating to the study type(s) and associated text words for the methodological description of the design(s).

*Date Restrictions*

Systematic database searches were initially conducted between April and November 2009 up to the most recent searchable date. Search updates were generated on a 6-monthly basis, with the final re-runs carried out 7 weeks before the guideline consultation. After this point, studies were only included if they were judged by the GDG to be exceptional (for example, if the evidence was likely to change a recommendation).

*Other Search Methods*

Other search methods involved scanning the reference lists of all eligible publications (systematic reviews, stakeholder evidence, and included studies) for more published reports and citations of unpublished research, sending lists of studies meeting the inclusion criteria to subject experts (identified through searches and by the GDG) and asking them to check the data for completeness, and provide information of any additional published or unpublished research for consideration (see Appendix 5 in the full version of the original guideline document for additional information). Tables of contents of key journals were checked for studies that might have been missed by the database and reference list searches, and key papers in the Science Citation Index (prospectively) were tracked over time for further useful references.

Full details of the search strategies and filters used for the systematic review of clinical evidence are provided in Appendix 8.

*Sifting*

After the initial search results were scanned liberally to exclude irrelevant papers, the review team used a purpose-built 'study information' database to manage both the included and the excluded studies (eligibility criteria were developed after consultation with the GDG). Double checking of all excluded studies was not done routinely, but a selection of abstracts was checked to ensure reliability of the sifting. For questions without good-quality evidence (after the initial search), a decision was made by the GDG about whether to: (i) repeat the search using subject-specific databases (for example, Education Resources Information Center [ERIC], Cambridge Scientific Abstracts [CSA] – Sociological Abstracts); (ii) conduct a new search for lower levels of evidence; or (iii) adopt a consensus process. Future guidelines will be able to update and extend the usable evidence base starting from the evidence collected, synthesised and analysed for this guideline.

*Study Selection*

All primary-level studies included after the first scan of citations were acquired in full and evaluated for eligibility as they were being entered into the study information database. More specific eligibility criteria were developed for each review question and are described in the relevant clinical evidence chapters in the full version of the original guideline document. Eligible systematic reviews and primary-level studies were critically

appraised for methodological quality (see Appendices 10 and 12 in the full version of the original guideline document). The eligibility of each study was confirmed by at least one member of the GDG. For some review questions, it was necessary to prioritise the evidence with respect to the UK context (that is, external validity).

*Unpublished Evidence*

The GDG used a number of criteria when deciding whether or not to accept unpublished data. First, the evidence must have been accompanied by a trial report containing sufficient detail to properly assess the quality of the data. Second, the evidence must have been submitted with the understanding that data from the study and a summary of the study's characteristics would be published in the full guideline. Therefore, the GDG did not accept evidence submitted as commercial in confidence. However, the GDG recognised that unpublished evidence submitted by investigators might later be retracted by those investigators if the inclusion of such data would jeopardise publication of their research.

Full details of the search strategies and filters used for the systematic review of clinical evidence are provided in Appendix 8 of the full version of the original guideline document.

See section 3.4 of the full version of the original guideline document for information on the Reference Manager and search filters.

Health Economics Methods

Systematic reviews of economic literature were conducted in all areas covered by the guideline. Economic modelling was undertaken in areas with likely major resource implications, where the current extent of uncertainty over cost-effectiveness was significant and economic analysis was expected to reduce this uncertainty, in accordance with the NICE guidelines manual. Prioritisation of areas for economic modelling was a joint decision between the health economist and the GDG. The rationale for prioritising review questions for economic modelling was set out in an economic plan agreed between NICE, the GDG, the health economist, and the other members of the technical team; the economic plan is presented in Appendix 14 of the full version of the original guideline document. The following economic questions were selected as key issues that were addressed by economic modelling:

- Cost-effectiveness of low and high-intensity psychological interventions for people with GAD
- Cost-effectiveness of pharmacological interventions for people with GAD
- Cost-effectiveness of CCBT for people with panic disorder

In addition, literature on the health-related quality of life of people with GAD and panic disorder was systematically searched to identify studies reporting appropriate health state utility scores that could be utilised in a cost-utility analysis.

Search Strategy for Economic Evidence

*Scoping Searches*

A broad preliminary search of the literature was undertaken in April 2009 to obtain an overview of the issues likely to be covered by the scope, and help define key areas. See section 3.6.1 of the full version of the original guideline document for additional information on scoping searches for economic evidence.

*Systematic Literature Searches*

After the review questions were formulated, a systematic search strategy was developed to locate all the relevant evidence. The balance between sensitivity (the power to identify all studies on a particular topic) and specificity (the ability to exclude irrelevant studies from the results) was carefully considered, and a decision made to utilise highly sensitive strategies to identify as complete a set as possible of relevant studies.

In order to ensure comprehensive coverage, search terms for GAD were kept purposely broad to help counter dissimilarities in bibliographic databases in thesaurus terms and indexing practices, and (often) imprecise reporting of study populations by authors in the titles and abstracts of records. It was observed that broader searching retrieved significantly more relevant records than would have been achieved through the use of more specific terms. A broad search for panic was similarly constructed for evidence relating to the effectiveness of CCBT.

A stepwise approach to formulising the searches was implemented at all times, and attempts made to eradicate duplication of effort in areas of overlapping coverage. Searches were restricted to economic studies and HTA reports, and conducted in the following databases:

- CINAHL
- EconLit
- EMBASE
- MEDLINE/MEDLINE In-Process

- PsycINFO
- HTA database
- NHS Economic Evaluation Database (EED)

Any relevant economic evidence arising from the clinical searches was also made available to the health economist during the same time frame.

*Date and Language Restrictions*

Systematic database searches were initially conducted between May and November 2009 up to the most recent searchable date. Search updates were generated on a 6-monthly basis, with the final re-runs carried out 7 weeks before the guideline consultation. After this point, studies were only included if they were judged by the GDG to be exceptional (for example, the evidence was likely to change a recommendation). Although no language restrictions were applied at the searching stage, foreign language papers were not requested or reviewed, unless they were of particular importance to an area under review. All the searches were restricted to research published from 1994 onwards. The date restriction was imposed in order to obtain data relevant to current healthcare settings and costs.

*Other Search Methods*

Other search methods involved scanning the reference lists of all eligible publications (systematic reviews, stakeholder evidence, and included studies from the economic and clinical reviews) to identify further studies for consideration.

Full details of the search strategies for the systematic review of health economic evidence are provided in Appendix 11 of the full version of the original guideline document.

*Inclusion Criteria for Economic Studies*

The following inclusion criteria were applied to select studies identified by the economic searches for further consideration:

- Only studies from Organisation for Economic Co-operation and Development countries were included, as the aim of the review was to identify economic information transferable to the UK context.
- Selection criteria based on types of clinical conditions and patients as well as interventions assessed were identical to the clinical literature review.
- Studies were included provided that sufficient details regarding methods and results were available to enable the methodological quality of the study to be assessed, and provided that the study's data and results were extractable.
- Full economic evaluations that compared two or more relevant options and considered both costs and consequences (that is, cost–consequence analysis, cost-effectiveness analysis, cost–utility analysis or cost–benefit analysis), as well as costing analyses that compared only costs between two or more interventions, were included in the review.
- Economic studies were included if they used clinical effectiveness data from an RCT, a cohort study, or a systematic review and meta-analysis of clinical studies. Studies that had a mirror-image design were excluded from the review.
- Studies were included only if the examined interventions were clearly described. This involved the dosage and route of administration and the duration of treatment in the case of pharmacological therapies; and the types of healthcare professionals involved as well as the frequency and duration of treatment in the case of psychological interventions. Evaluations in which medications were treated as a class were excluded from further consideration.

See section 3.6 of the full version of the original guideline document for information on the Reference Manager, search filters, and results of the systematic search.

## Number of Source Documents

Not stated

## Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Weighting According to a Rating Scheme (Scheme Given)

## Rating Scheme for the Strength of the Evidence

The quality of the evidence was based on the quality assessment components (study design, limitations to study quality, consistency, directness, and any other considerations) and graded using the following definitions:

- High: Further research is very unlikely to change confidence in the estimate of the effect
- Moderate: Further research is likely to have an important impact on confidence in the estimate of the effect and may change the estimate
- Low: Further research is very likely to have an important impact on confidence in the estimate of the effect and is likely to change the estimate
- Very low: Any estimate of effect is very uncertain

## Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

## Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Collaborating Centre for Mental Health on behalf of the National Institute for Health and Clinical Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

Systematic Clinical Literature Review

Data Extraction

Study characteristics and outcome data were extracted from all eligible studies, which met the minimum quality criteria, using a bespoke database and Review Manager.

See section 3.5.5 of the full version of the original guideline document for additional information on data extraction.

The meta-analysis of survival data, such as time to any mood episode, was based on log hazard ratios and standard errors. Since individual patient data were not available in included studies, hazard ratios and standard errors calculated from a Cox proportional hazard model were extracted. Where necessary, standard errors (SEs) were calculated from confidence intervals (CIs) or p-value according to standard formulae. Data were summarised using the generic inverse variance method using Review Manager.

Consultation with another reviewer or members of the Guideline Development Group (GDG) was used to overcome difficulties with coding. Data from studies included in existing systematic reviews were extracted independently by one reviewer and cross-checked with the existing dataset. Where possible, two independent reviewers extracted data from new studies. Where double data extraction was not possible, data extracted by one reviewer were checked by the second reviewer. Disagreements were resolved with discussion. Where consensus could not be reached, a third reviewer or GDG members resolved the disagreement. Masked assessment (that is, blind to the journal from which the article comes, the authors, the institution and the magnitude of the effect) was not used since it is unclear that doing so reduces bias.

Synthesising the Evidence

Where possible, meta-analysis was used to synthesise the evidence using Review Manager. If necessary, reanalyses of the data or sub-analyses were used to answer review questions not addressed in the original studies or reviews.

Dichotomous outcomes were analysed as relative risks (RR) with the associated 95% confidence interval (CI).

Continuous outcomes were analysed using the mean difference (MD), or standardised mean difference (SMD) when different measures were used in different studies to estimate the same underlying effect. If reported by study authors, intention-to-treat data, using a method such as 'last observation carried forward', were preferred over data from completers.

To check for consistency of effects among studies, both the $I^2$ statistic and the chi-squared test of heterogeneity, as well as a visual inspection of

the forest plots were used.

Two factors were used to make a judgement about importance of the observed value of $I^2$: (i) the magnitude and direction of effects, and (ii) the strength of evidence for heterogeneity (for example, p-value from the chi-squared test, or a confidence interval for $I^2$).

*Publication Bias*

To explore the possibility that the results entered into each meta-analysis suffered from publication bias, data from included studies were entered, where there was sufficient data, into a funnel plot. Asymmetry of the plot was taken to indicate possible publication bias and investigated further. Where necessary, an estimate of the proportion of eligible data that were missing (because some studies did not include all relevant outcomes) was calculated for each analysis.

Included/excluded studies tables, generated automatically from the study database, were used to summarise general information about each study (see Appendix 15b–e of the full version of the original guideline document). Where meta-analysis was not appropriate and/or possible, the reported results from each primary-level study were also presented in the included studies table (and included, where appropriate, in a narrative review).

See section 3.5.6 of the full version of the original guideline document for additional information on synthesis of the evidence.

Presenting the Data to the Guideline Development Group

Study characteristics tables and, where appropriate, forest plots generated with Review Manager were presented to the guideline development group (GDG) in order to prepare a Grading of Recommendations Assessment, Development, and Evaluation (GRADE) evidence profile table for each review and to develop recommendations. See section 3.5.7 in the full version of the original guideline document for additional information.

Forming the Clinical Summaries

Once the GRADE evidence profiles relating to a particular review question were completed, summary evidence tables were developed (these tables are presented in the evidence chapters in the full version of the original guideline document). Finally, the systematic reviewer in conjunction with GDG members produced a clinical evidence summary.

Health Economics Methods

Applicability and Quality Criteria for Economic Studies

All economic papers eligible for inclusion were appraised for their applicability and quality using the methodology checklist for economic evaluations recommended by the NICE guidelines manual (NICE, 2009), which is shown in Appendix 12 of the full version of the guideline. The methodology checklist for economic evaluations was also applied to the economic models developed specifically for this guideline. All studies that fully or partially met the applicability and quality criteria described in the methodology checklist were considered during the guideline development process, along with the results of the economic modelling conducted specifically for this guideline. The completed methodology checklists for all economic evaluations considered in the guideline are provided in Appendix 17 of the full version of the guideline.

Presentation of Economic Evidence

The references to included studies from the economics literature review as well as the evidence tables with the characteristics and results of economic studies included in the review, are provided in Appendix 15f of the full version of the original guideline document. Methods and results of economic modelling undertaken alongside the guideline development process are presented in the relevant evidence chapters in the full version of the original guideline document. Characteristics and results of all economic studies considered during the guideline development process (including modelling studies conducted for this guideline) are summarised in economic evidence profiles accompanying respective GRADE clinical evidence profiles in Appendix 18 of the full version of the original guideline document.

## Methods Used to Formulate the Recommendations

Expert Consensus

Informal Consensus

## Description of Methods Used to Formulate the Recommendations

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Collaborating Centre for Mental Health (NCCMH) on behalf of the National Institute for Health and Clinical Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

The Guideline Development Group (GDG)

The GDG consisted of professionals in psychiatry, clinical psychology, nursing and general practice, academic experts in psychiatry and psychology, and service user and carer representatives from service user and carer organisations. The guideline development process was supported by staff from the NCCMH, who undertook the clinical and health economics literature searches, reviewed and presented the evidence to the GDG, managed the process, and contributed to drafting the guideline.

*Guideline Development Group Meetings*

Eleven GDG meetings were held between June 2009 and September 2010. During each day-long GDG meeting, in a plenary session, review questions and clinical and economic evidence were reviewed and assessed, and recommendations formulated. At each meeting, all GDG members declared any potential conflicts of interest, and service user and carer concerns were routinely discussed as part of a standing agenda.

*Topic Groups*

The GDG divided its workload along clinically relevant lines to simplify the guideline development process, and certain GDG members were asked to undertake guideline work in that area of clinical practice. As the GDG was relatively small, there were no defined topic groups for the clinical evidence on pharmacological and psychological interventions; however there was a topic group that looked at service user and carer experience through personal accounts and qualitative literature. This group managed the evidence appraisal prior to presenting it to the GDG as a whole.

*Service Users and Carers*

Individuals with direct experience of services gave an integral service-user focus to the GDG and the guideline. The GDG included service user and carer representatives who contributed as full GDG members to writing the review questions, helping to ensure that the evidence addressed their views and preferences, highlighting sensitive issues and terminology relevant to the guideline, and bringing service-user research to the attention of the GDG. In drafting the guideline, they contributed to writing the guideline's introduction (Chapter 2 of the full version of the original guideline document) and the review of experience of care (Chapter 4 of the full version of the original guideline document), and they identified recommendations from the service user and carer perspective.

*National and International Experts*

National and international experts in the area under review were identified through the literature search and through the experience of the GDG members. These experts were contacted to recommend unpublished or soon-to-be published studies in order to ensure up-to-date evidence was included in the development of the guideline. They informed the group about completed trials at the pre-publication stage, systematic reviews in the process of being published, studies relating to the cost-effectiveness of treatment and trial data if the GDG could be provided with full access to the complete trial report. Appendix 5 of the full version of the original guideline document lists researchers who were contacted.

Forming the Recommendations

After the Grading of Recommendations Assessment, Development and Evaluation (GRADE) profiles and clinical summaries were presented to the GDG, the associated recommendations were drafted. In making recommendations, the GDG took into account the trade-off between the benefits and downsides of treatment as well as other important factors, such as economic considerations, social value judgements, the requirements to prevent discrimination and to promote equality, and the GDG's awareness of practical issues.

Finally, to show clearly how the GDG moved from the evidence to the recommendations, each chapter in the full version of the original guideline document has a section called 'from evidence to recommendations'. Underpinning this section is the concept of the 'strength' of a recommendation. This takes into account the quality of the evidence but is conceptually different. Some recommendations are 'strong' in that the GDG believes that the vast majority of healthcare professionals and patients would choose a particular intervention if they considered the evidence in the same way that the GDG has. This is generally the case if the benefits clearly outweigh the harms for most people and the intervention is likely to be cost effective. However, there is often a closer balance between benefits and harms, and some patients would not choose an intervention whereas others would. This may happen, for example, if some patients are particularly averse to some side effect and others are not. In these circumstances the recommendation is generally weaker, although it may be possible to make stronger recommendations about specific groups of patients. The strength of each recommendation is reflected in the wording of the recommendation, rather than by using labels or symbols.

Method Used to Answer a Review Question in the Absence of Appropriately Designed, High-Quality Research

In the absence of appropriately designed, high-quality research, or where the GDG were of the opinion (on the basis of previous searches or their knowledge of the literature) that there was unlikely to be such evidence, an informal consensus process was adopted. This process focused on those questions that the GDG considered a priority.

*Informal Consensus*

The starting point for the process of informal consensus was that members of the GDG identified, with help from the systematic reviewer, a narrative review that most directly addressed the review question. Where this was not possible, a brief review of the recent literature was initiated.

This existing narrative review or new review was used as a basis for beginning an iterative process to identify lower levels of evidence relevant to the review question and to lead to written statements for the guideline. The process involved a number of steps:

1. A description of what is known about the issues concerning the review question was written by one of the GDG members.
2. Evidence from the existing review or new review was then presented in narrative form to the GDG and further comments were sought about the evidence and its perceived relevance to the review question.
3. Based on the feedback from the GDG, additional information was sought and added to the information collected. This may include studies that did not directly address the review question but were thought to contain relevant data.
4. If, during the course of preparing the report, a significant body of primary-level studies (of appropriate design to answer the question) were identified, a full systematic review was done.
5. At this time, subject possibly to further reviews of the evidence, a series of statements that directly addressed the review question were developed.
6. Following this, on occasions and as deemed appropriate by the GDG, the report was then sent to appointed experts outside the GDG for peer review and comment. The information from this process was then fed back to the GDG for further discussion of the statements.
7. Recommendations were then developed and could also be sent for further external peer review.
8. After this final stage of comment, the statements and recommendations were again reviewed and agreed upon by the GDG.

## Rating Scheme for the Strength of the Recommendations

Not applicable

## Cost Analysis

The economic evidence considered in the guideline is provided in the respective evidence chapters, following presentation of the relevant clinical evidence in the full version of the original guideline document. The references to included studies as well as the evidence tables with the characteristics and results of economic studies included in the review are provided in Appendix 15f of the full version of the original guideline document. Methods and results of economic modelling undertaken alongside the guideline development process are presented in the relevant evidence chapters in the full version of the original guideline document. Characteristics and results of all economic studies considered during the guideline development process (including modelling studies conducted for this guideline) are summarised in economic evidence profiles accompanying respective Grades of Recommendation Assessment, Development and Evaluation (GRADE) clinical evidence profiles in Appendix 18 of the full version of the original guideline document.

## Method of Guideline Validation

External Peer Review

Internal Peer Review

## Description of Method of Guideline Validation

Registered stakeholders had an opportunity to comment on the draft guideline, which was posted on the National Institute for Health and Clinical Excellence (NICE) website during the consultation period. Following the consultation, all comments from stakeholders and others were responded to, and the guideline updated as appropriate. The Guidelines Review Panel (GRP) also reviewed the guideline and checked that stakeholders' comments had been addressed. Following the consultation period, the Guideline Development Group (GDG) finalised the recommendations and the National Collaborating Centre for Mental Health (NCCMH) produced the final documents. These were then submitted to NICE. NICE then

formally approved the guideline and issued its guidance to the National Health Service (NHS) in England and Wales.

# Evidence Supporting the Recommendations

## Type of Evidence Supporting the Recommendations

The type of supporting evidence supporting the recommendations is not specifically stated.

# Benefits/Harms of Implementing the Guideline Recommendations

## Potential Benefits

Appropriate management of generalised anxiety disorder and panic disorder (with or without agoraphobia)

## Potential Harms

- The main adverse events associated with antidepressants are cardiovascular symptoms, bleeding, gastrointestinal symptoms, sexual dysfunction, weight change, and suicidal ideation and behaviour.
- There was consistent evidence that selective serotonin reuptake inhibitors (SSRIs) were associated with an increased risk of gastrointestinal bleeding particularly in elderly people. Although such events were relatively rare, the guideline development group considered this was still important to take into account when considering prescribing an SSRI. In addition, there was evidence that antidepressant use was associated with an increased probability of suicidal behaviour in participants under 25 years of age.
- All SSRIs have been implicated in the development of serotonin syndrome, a potentially life threatening complication.
- Serotonin noradrenaline reuptake inhibitors (SNRIs) carry a risk of increasing blood pressure.

For additional information on side effects of pharmacological interventions see section 8.7 of the full version of the original guideline document.

# Contraindications

## Contraindications

Benzodiazepines are not recommended because of the potential for the development of tolerance and dependence in a condition where treatment may need to be given for several months but are still in relatively wide use.

# Qualifying Statements

## Qualifying Statements

- The guideline assumes that prescribers will use a drug's summary of product characteristics (SPC) to inform their decisions made with individual service users.
- This guideline recommends some drugs for indications for which they do not have a UK marketing authorisation at the date of publication, if there is good evidence to support that use. Where recommendations have been made for the use of drugs outside their licensed indications ('off-label use'), this is indicated in the recommendation or in a footnote.

# Implementation of the Guideline

# Description of Implementation Strategy

The National Institute for Health and Clinical Excellence (NICE) has developed tools to help organisations implement this guidance. These are available on the NICE Web site (http://guidance.nice.org.uk/CG113 ; see also the "Availability of Companion Documents" field).

Key Priorities for Implementation

The following recommendations have been identified as priorities for implementation. They have been chosen from the updated recommendations on the management of generalised anxiety disorder (GAD).

Step 1: All Known and Suspected Presentations of GAD

*Identification*

- Identify and communicate the diagnosis of GAD as early as possible to help people understand the disorder and start effective treatment promptly. [new 2011]
- Consider the diagnosis of GAD in people presenting with anxiety or significant worry, and in people who attend primary care frequently who:
  - Have a chronic physical health problem or
  - Do not have a physical health problem but are seeking reassurance about somatic symptoms (particularly older people and people from minority ethnic groups) or
  - Are repeatedly worrying about a wide range of different issues [new 2011]

Step 2: Diagnosed GAD That Has Not Improved after Step 1 Interventions

*Low-Intensity Psychological Interventions for GAD*

- For people with GAD whose symptoms have not improved after education and active monitoring in step 1, offer one or more of the following as a first-line intervention, guided by the person's preference:
  - Individual non-facilitated self-help
  - Individual guided self-help
  - Psychoeducational groups [new 2011]

Step 3: GAD with Marked Functional Impairment or That Has Not Improved after Step 2 Interventions

*Treatment Options*

- For people with GAD and marked functional impairment, or those whose symptoms have not responded adequately to step 2 interventions:
  - Offer either:
    - An individual high-intensity psychological intervention or
    - Drug treatment
  - Provide verbal and written information on the likely benefits and disadvantages of each mode of treatment, including the tendency of drug treatments to be associated with side effects and withdrawal syndromes.
  - Base the choice of treatment on the person's preference as there is no evidence that either mode of treatment (individual high-intensity psychological intervention or drug treatment) is better. [new 2011]

*High-Intensity Psychological Interventions*

- If a person with GAD chooses a high-intensity psychological intervention, offer either cognitive behavioural therapy (CBT) or applied relaxation. [new 2011]

*Drug Treatment*

- If a person with GAD chooses drug treatment, offer a selective serotonin reuptake inhibitor (SSRI). Consider offering sertraline first because it is the most cost-effective drug, but note that at the time of publication (January 2011) sertraline did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented. Monitor the person carefully for adverse reactions. [new 2011]
- Do not offer a benzodiazepine for the treatment of GAD in primary or secondary care except as a short-term measure during crises. Follow

the advice in the 'British national formulary' on the use of a benzodiazepine in this context. [new 2011]
- Do not offer an antipsychotic for the treatment of GAD in primary care. [new 2011]

*Inadequate Response to Step 3 Interventions*

- Consider referral to step 4 if the person with GAD has severe anxiety with marked functional impairment in conjunction with:
  - A risk of self-harm or suicide or
  - Significant comorbidity, such as substance misuse, personality disorder or complex physical health problems or
  - Self-neglect or
  - An inadequate response to step 3 interventions. [new 2011]

## Implementation Tools

Audit Criteria/Indicators

Foreign Language Translations

Patient Resources

Quick Reference Guides/Physician Guides

Resources

Slide Presentation

Staff Training/Competency Material

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

# Institute of Medicine (IOM) National Healthcare Quality Report Categories

## IOM Care Need

Getting Better

Living with Illness

## IOM Domain

Effectiveness

Patient-centeredness

# Identifying Information and Availability

## Bibliographic Source(s)

National Collaborating Centre for Mental Health, National Collaborating Centre for Primary Care. Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults. Management in primary, secondary and community care. London (UK): National Institute for Health and Clinical Excellence (NICE); 2011 Jan. 56 p. (Clinical guideline; no. 113).

## Adaptation

Not applicable: The guideline was not adapted from another source.

## Date Released

2004 Dec (revised 2011 Jan)

## Guideline Developer(s)

National Collaborating Centre for Mental Health - National Government Agency [Non-U.S.]

National Collaborating Centre for Primary Care - National Government Agency [Non-U.S.]

## Source(s) of Funding

National Institute for Health and Clinical Excellence (NICE)

## Guideline Committee

Guideline Development Group

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## Financial Disclosures/Conflicts of Interest

All GDG members made formal declarations of interest at the outset, which were updated at every GDG meeting. Declarations of interest can be found in Appendix 3 of the full version of the original guideline.

## Guideline Status

This is the current release of the guideline.

This guideline updates previous versions:

McIntosh A, Cohen A, Turnbull N, Esmonde L, Dennis P, Eatock J, Feetam C, Hague J, Hughes I, Kelly J, Kosky N, Lear G, Owens L, Ratcliffe J, Salkovskis P. Clinical guidelines for the management of anxiety. Management of anxiety (panic disorder, with or without agoraphobia, and generalised anxiety disorder) in adults in primary, secondary and community care. London (UK): National Institute for Clinical Excellence (NICE); 2004 Dec. 165 p.

National Collaborating Centre for Primary Care. Anxiety: management of anxiety (panic disorder, with or without agoraphobia, and generalised anxiety disorder) in adults in primary, secondary and community care. London (UK): National Institute for Clinical Excellence (NICE); 2007 Apr. 54 p. (Clinical guideline; no. 22).

## Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) format from the National Institute for Health and Clinical Excellence (NICE) Web site.

## Availability of Companion Documents

The following are available:

- Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults. Management in primary, secondary and community care. Quick reference guide. London (UK): National Institute for Health and Clinical Excellence; 2011 Jan. 24 p. (Clinical guideline; no. 113). Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site.
- Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults. Management in primary, secondary and community care. Full guideline. London (UK): National Institute for Health and Clinical Excellence (NICE); 2011. 463 p. (Clinical guideline; no. 113). Electronic copies: Available in PDF format from the NICE Web site.
- Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults. Management in primary, secondary and community care. Appendices to full version. London (UK): National Institute for Health and Clinical Excellence; 2011. Various p. (Clinical guideline; no. 113). Electronic copies: Available in PDF from the NICE Web site.
- Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults. Costing statement. London (UK): National Institute for Health and Clinical Excellence; 2011. 9 p. (Clinical guideline; no. 113). Electronic copies: Available in PDF from the NICE Web site.
- Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults. Costing template. London (UK): National Institute for Health and Clinical Excellence; 2011 Jan. (Clinical guideline; no. 113). Electronic copies: Available in PDF from the NICE Web site.
- Generalised anxiety disorder in adults. Slide set. London (UK): National Institute for Health and Clinical Excellence; 2011. (Clinical guideline; no. 113). Electronic copies: Available from the NICE Web site.
- Generalised anxiety disorder and panic disorder in adults. Audit support. Clinical criteria. London (UK): National Institute for Health and Clinical Excellence; 2011. 12 p. (Clinical guideline; no. 113). Electronic copies: Available from the NICE Web site.
- Generalised anxiety disorder and panic disorder in adults. Audit support. Information and support criteria. London (UK): National Institute for Health and Clinical Excellence; 2011. 17 p. (Clinical guideline; no. 113). Electronic copies: Available from the NICE Web site.
- Clinical case scenarios for generalised anxiety disorder for use in primary care. London (UK): National Institute for Health and Clinical Excellence; 2011. 23 p. (Clinical guideline; no. 113). Electronic copies: Available in PDF from the NICE Web site.
- Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults. Educational resource. Slide set. London (UK): National Institute for Health and Clinical Excellence; 2011. 23 p. (Clinical guideline; no. 113). Electronic copies: Available from the NICE Web site.
- Generalised anxiety disorder and panic disorder. Baseline assessment tool. London (UK): National Institute for Health and Clinical Excellence; 2011. Various p. (Clinical guideline; no. 113). Electronic copies: Available from the NICE Web site.
- Anxiety: treatment manuals for cognitive behavioural therapy and applied relaxation. London (UK): National Institute for Health and Clinical Excellence; 2011. 3 p. (Clinical guideline; no. 113). Electronic copies: Available from the NICE Web site.
- The guidelines manual 2009. London (UK): National Institute for Health and Clinical Excellence (NICE); 2009 Jan. Electronic copies:

Available in Portable Document Format (PDF) from the NICE Archive Web site.

## Patient Resources

The following is available:

- Treating generalised anxiety disorder and panic disorder in adults. Understanding NICE guidance - information for people who use NHS services. National Institute for Clinical Excellence (NICE); 2011 Jan. 16 p. Available from the National Institute for Health and Clinical Excellence (NICE) Web site. Also available in Welsh from the NICE Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

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